

### REMARKS

Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

An unexecuted copy of a DECLARATION under 37 C.F.R. § 1.132 of Manuel Vega was submitted with the Response and Amendment mailed October 4, 2007 in response to the Office Action mailed April 4, 2007. The executed DECLARATION of Manuel Vega is attached hereto. The executed DECLARATION is identical to the unexecuted copy, except for minor differences in the bibliographic information of Dr. Manuel Vega. For example, the executed DECLARATION is updated to indicate that Manuel Vegas has been Chief Executive Officer of Nautilus Biotech since January 2000 and until August 2007. Also, the executed DECLARATION indicates that Manuel Vega was an adjunct Professor of Human Gene Therapy and of Molecular Genetics at Universidad Nacional del Sur (UNS). Further, the DECLARATION is updated to indicate that the Universidasd Nacional del Sur (UNS) is located in Bahia Blanca, Argentina.

### DECLARATION

As discussed in the response, mailed October 4, 2007, the DECLARATION of Dr. Manuel Vega is provided to demonstrate that interferon alpha cytokines exhibit properties not taught or suggested by the cited references nor any references of record. The DECLARATION demonstrates: (1) increased resistance to protease does not require modification of all protease cleavage sites; (2) modification can be achieved without substantially altering a desired biological activity; (3) polypeptides, which are not orally available, become so upon modification to exhibit increased protease resistance; and (4) the polypeptides modified to exhibit increased resistance to proteases also exhibit increase serum stability and half-life.

In particular, the DECLARATION shows that modification of as few as a single residue (see Table 1), such as E41Q, results in a polypeptide that exhibits increased protease resistance. Such resistance is not necessarily resistance to a particular protease, but to a variety of proteases. The DECLARATION demonstrates that when modified based on the property of increased protease resistance, the cytokines exhibit increased resistance to proteases *in vitro* and *in vivo*. For example, as described in the application and as provided in the DECLARATION, exemplary candidate LEAD polypeptides tested for proteolysis against

a cocktail of proteases *in vitro* exhibited increased proteolysis compared to an IFN $\alpha$ -2b not containing the modification.

The DECLARATION also demonstrates that the resulting modified cytokines can retain original activity. As described in the DECLARATION, the results show that the exemplary mutant E41Q in IFN $\alpha$ 2b not only exhibits increased protease resistance to a cocktail of proteases, but also to blood lysate, serum and to chymotrypsin. Thus, the amino acid replacement confers increased protease resistance of the cytokine across the entire molecule, which increased resistance is not specific to a particular protease.

In the DECLARATION, data also are provided to demonstrate that the proteins exhibit improved pharmacokinetics upon subcutaneous and oral administration compared to proteins not containing the amino acid replacement(s). For example, the DECLARATION provides data demonstrating that a mutant IFN- $\alpha$  containing only a single amino acid mutation (E41Q), when administered subcutaneously or orally, retains anti-viral activity in the serum for a longer time period than the native polypeptide. In addition, the result show that SuperLEADs, containing two or more amino acid changes described in the above-captioned application, also exhibit similar increases in half-life. Thus, an IFN- $\alpha$ , containing in many instances only a single amino acid replacement to render the cytokine protease resistance, can be used as a therapeutic due to the improved properties compared to the native polypeptide.

In the case of per-oral administration, the native polypeptide retains **no** detectable activity when administered; whereas, the IFN- $\alpha$  with a single amino acid change, can be successfully administered orally. For example, Figure 3 shows that unmodified interferon alpha cannot be administered orally; whereas, a modified form, with only a single amino acid change can be administered orally and exhibit anti-viral activity in the serum. This really is astounding, and of enormous medical and economic value. Therefore, the results provided in the DECLARATION show that the interferon alpha cytokines as claimed have properties that are not taught or suggested by any of the cited references.

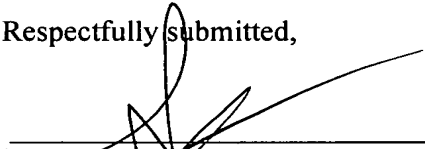
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Applicant : Rene Gantier *et al.*  
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Supplemental Response

In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,



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